JC20 Rec'd PCT/PTO 14 AUG 2001

FORM PTO-1390 (REV. 11-2000) U S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY 'S DOCKET NUMBER: GJE-74

U S APPLICATION NO (If known, see 37 CFR 1 5): 09/913443

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/GB00/00636	23 February 2000	24 February 1999

TITLE OF INVENTION: Transplantation Of Haematopoietic Cells

APPLICANT(S) FOR DO/EO/US: Jack Price

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☑ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.
4. ☐ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☑ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is attached hereto (required only if not communicated by the International Bureau).
   b. ☑ has been communicated by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☐ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☐ Amendments to the claims of the International Aplication under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9. ☑ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ An English lanugage translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 to 20 below concern document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☑ A FIRST preliminary amendment.
14. ☐ A SECOND or SUBSEQUENT preliminary amendment.
15. ☐ A substitute specification.
16. ☐ A change of power of attorney and/or address letter.
17. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 37 CFR 1.821 - 1.825.
18. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
19. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
20. ☐ Other items or information:

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U.S. APPLICATION NO (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
09/913443	PCT/GB00/00636	GJE-74

21. ☑ The following fees are submitted:

	CALCULATIONS PTO USE ONLY	
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)):		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO **$1000.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$860.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO **$710.00**		
International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$690.00**		
International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) **$100.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$860.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).		

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	$
Total claims	12 - 20 =	0	x **$18.00**	
Independent claims	2 - 3 =	0	x **$80.00**	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ **$270.00**	

TOTAL OF ABOVE CALCULATIONS =	$860.00	
☐ Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2. +		
SUBTOTAL =	$860.00	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)).		
TOTAL NATIONAL FEE =	$860.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +		
TOTAL FEES ENCLOSED =	$860.00	
	Amount to be refunded:	$
	charged:	$

a. ☐ A check in the amount of $ _____ to cover the above fees is enclosed.

b. ☑ Please charge my Deposit Account No. 19-0065 in the amount of $ 860.00 to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☑ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 19-0065 . A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137 (a) or (b)) must be filed and granted to restore the application to pending status.

CORRESPONDENCE ADDRESS:

CUSTOMER NUMBER
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David Saliwanchik
SIGNATURE

August 14, 2001
DATE

David R. Saliwanchik
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REGISTRATION NUMBER

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09/913443

August 14, 2001

Patent Application
Docket No. GJE-74

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s) : Jack Price

Docket No. : GJE-74

For : Transplantation of Haematopoietic Cells

PRELIMINARY AMENDMENT

The following amendments are made with respect to the specification and claims in the international application PCT/GB00/00636.

In the Specification

After page 8: Please insert as new page 9 the attached Abstract of the Disclosure.

In the claims

Please substitute the following claims:

Claim 1 (amended):

A method for treating a sensory, motor and/or cognitive deficit wherein said method comprises the intracerebral administration of a haemapopietic stem cell to a patient in need of such treatment.

Claim 2 (amended):

The method, according to claim 1, which comprises intracerebral transplantation of said stem cell into a damaged brain.

Claim 3 (amended):

The method, according to claim 1, wherein the treatment is for a condition selected from the group consisting of Alzheimer's disease, Parkinson's disease, Korsakoff's disease and Creuzfeld-Jacob disease.

Claim 4 (amended):

The method, according to claim 1, wherein said haematopoietic stem cell is conditionally immortal.

Claim 5 (amended):

The method, according to claim 4, wherein said cell comprises a temperature sensitive oncogene which is not expressed at a temperature above 35 C.

Claim 6 (amended):

The method, according to claim 5, wherein said onocogene expresses the SV40 T-antigen.

Claim 7 (amended):

The method, according to claim 1, wherein said haematopoietic stem cell is genetically transformed to express a therapeutic heterologous gene product.

Please cancel claims 8 and 9 and add the following new claims:

10. A pharmaceutical composition for treating a sensory, motor and/or cognitive deficit, wherein said composition comprises a haematopoietic stem cell and a pharmaceutically acceptable carrier.

11. The composition, according to claim 10, wherein said haematopoietic stem cell is conditionally immortal.

12. The composition, according to claim 11, wherein the cell comprises a temperature sensitive oncogene which is not expressed at a temperature above 35°C.

13. The composition, according to claim 12, wherein the oncogene expresses SV40 T-antigen.

14. The composition, according to claim 10, wherein the haematopoietic stem cell is genetically transformed to express a therapeutic heterologous gene product.

Remarks

By this Amendment, claims 1-7 have been amended; claims 8 and 9 have been canceled and new claims 10-14 have been added.

No new matter has been added by these amendments.

The Commissioner is hereby authorized to charge any fees under 37 CFR 1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

Respectfully Submitted

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DRS/la

Attachment: Marked-up Version of Amended claims
Abstract (page 9)

Certificate of Mailing

Marked-up Version of Amended Claims

Claim 1 (amended):

[Use] A method for treating a sensory, motor and/or cognitive deficit wherein said method comprises the intracerebral administration of a haemapopietic stem cell to a patient in need of such treatment [of a haematopoietic stem cell in the manufacture of a medicament for the treatment of a sensory, motor and/or cognitive deficit].

Claim 2 (amended):

[Use] The method, according to claim 1, which comprises [for] intracerebral transplantation of said stem cell into a damaged brain.

Claim 3 (amended):

[Use] The method, according to claim 1[or claim 2], wherein the treatment is for a condition selected from the group consisting of Alzheimer's disease, Parkinson's disease, Korsakoff's disease [or] and Creuzfeld-Jacob disease.

Claim 4 (amended):

[Use] The method, according to [any preceding claim] claim 1, wherein [the] said haematopoietic stem cell is conditionally immortal.

Claim 5 (amended):

[Use] The method, according to claim 4, wherein [the] said cell comprises a temperature sensitive oncogene which is not expressed at a temperature above 35 C.

Claim 6 (amended):

[Use] The method, according to claim 5, wherein [the] said onocogene expresses the SV40 T- antigen.

Claim 7 (amended):

[Use] The method, according to [any preceding claim] claim 1, wherein [the] said haematopoietic stem cell is genetically transformed to express a therapeutic heterologous gene product.

Replacement Sheet

Abstract of the Disclosure

Transplantation of haematopoietic stem cells is proposed for the treatment of a damaged brain. Intracerebral transplantation of haematopoietic stem cells may repair function and may be suitable for treatment of Alzheimer's disease, Parkinson's disease and Creuzfeld-Jacob disease.

TRANSPLANTATION OF HAEMATOPOIETIC CELLS

Field of the Invention

The present invention relates to the correction of sensory, motor and/or cognitive deficits by the intracerebral transplantation of cells, and to cells and medicaments therefor.

Background to the Invention

Sensory, motor and/or cognitive deficits are caused by many diseases and may also be caused when the brain undergoes trauma. For example, motor dysfunction is one symptom of Parkinson's disease. As yet, in most cases, there is no satisfactory treatment available.

Bjornson *et al*, Science (1999) 283:534-537, describes the ability of neural stem cells to produce a variety of blood cell types, including myeloid, lymphoid and haematopoietic cells. It is believed that the neural stem cells contain appropriate mechanisms required to express otherwise silent genetic information to respond to signals that normally stimulate blood stem cells. The experiment suggests that the adult blood system contains powerful signals that "activate" the neural stem cells.

Haematopoietic cells are the progenitor cells for all of the blood cells, including leukocytes and erythrocytes. The transplantation of such cells has been proposed, for example, in WO-A-92/11355, in connection with haematopoietic disorders, including sickle cell anaemia and haemophilia. Methods for culturing and genetically altering haematopoietic stem cells are disclosed in WO-A-92/11355 and WO-A-93/18137.

Summary of the Invention

The present invention is based in part on the observation that, when transplanted into a damaged or diseased brain, haematopoietic stem cells appear to respond to signals from the damaged or diseased brain by taking up a phenotype that is able to replace or compensate for functional deficits to which the damage or disease otherwise leads.

For use in the present invention, the haematopoietic stem cells should be capable of differentiating into cells appropriate to repair or compensate for

the damage or disease in the target area of the brain. It will be appreciated that cells for transplantation need not be capable of differentiation into all types or phenotypes of neural cells.

The treatment may be carried out on any mammal but the present invention is especially concerned with the treatment of humans, especially treatment with human cells, and with human cells and cell lines.

The cells of the present invention are capable of correcting a sensory, motor and/or cognitive deficit when implanted into a damaged part of the human brain. The term "damage" used herein includes reduction or loss of function. The term also includes cell loss. Damage may be caused by any of a variety of means including physical trauma, hypoxia (lack of oxygen), chemical agents, for example, damage may be caused by drug abuse, and disease. The following diseases and pathological conditions are examples of diseases or conditions which result in sensory, motor and/or cognitive deficits which may be treated in accordance with the present invention: traumatic brain injury, stroke, perinatal ischaemia, including cerebral palsy, Alzheimer's, Pick's and related dementing neurodegenerative diseases, multi-infarct dementia, Parkinson's and Parkinson's type diseases, Huntington's disease, Korsakoff's disease and Creuzfeld-Jacob disease. Amnesia, particularly following transitory global ischaemia such as after cardiac arrest or coronary bypass surgery, may also be treated in accordance with the present invention.

The cells may also be administered to sites distant from the actual site of damage, for example, the cells may be administered to the contra-lateral region from that exhibiting damage.

The present invention provides for the use of haematopoietic stem cells, optionally in isolated form, in the manufacture of a medicament for the treatment of a sensory, motor and/or cognitive deficit. The medicament to be administered comprises haematopoietic stem cells.

The present invention further provides for the use of conditionally immortal, haematopoietic stem cells in the manufacture of a medicament for the

treatment of a sensory, motor and/or cognitive deficit. The medicament to be administered comprises conditionally immortal, haematopoietic stem cells.

The conditionally immortal cells according to, and used in, the present invention may be from clonal cell lines or may be of mixed population. Cells from clonal cell lines may be preferred. Cells from a single cell line may be used or a mixture of cells from two or more cell lines may be used.

The invention further provides a pharmaceutical preparation comprising cells according to the invention and a pharmaceutically acceptable carrier.

Description of the Invention

The present invention is based on the realisation that when haematopoietic stem cells are implanted into a damaged brain, the cells surprisingly differentiate into a form of cell that is capable of repairing the damage and improve function. The phenotype of the differentiated cells may be the same as the phenotype of the damaged or lost cells, however, the differentiated cells may be of a different phenotype, or of a number of phenotypes. In any case, the cells take up a phenotype that is capable of functionally integrating and compensating for the damaged or lost cells. That is assisted by the propensity, that we have discovered, of the cells to migrate to, and seek out, damaged tissue.

The use of stem cells means that with one clonal cell line it is possible to repair damage in a number of different areas of the brain. It also means that if more than one particular cell type is required to repair damage in a given area then a single cell line will be capable of differentiating into the different types of cells required.

Conditionally immortal cells are cells which are immortal under certain permissive conditions but are not immortal under nonpermissive conditions. In the present case this means that by conditionally immortalising the stem cells and maintaining them under permissive conditions the development of the stem cells may be arrested at a chosen stage and they may be propagated for long periods. Use of conditionally immortalisation allows the development of clonal lines which are readily expandable in vitro. If the conditions under which the

cells are maintained are switched to nonpermissive conditions, the development of the cells is allowed to continue. If the correct conditions are provided the cells will continue to develop and will differentiate.

Immortalised cells are usually prepared by the transduction of an oncogene into cells. There is therefore a risk of tumour formation in the long term, so such cells are not preferred for use in the present invention.

Conditionally immortal cells have the advantages of immortal cells in that they are "frozen" in the desired stage of development, are easily maintained and multiply well when under permissive conditions but they may be used in transplants as long as the environment into which they are transplanted has nonpermissive conditions. In the case of the cells of the present invention the gene used to confer conditional immortality should be chosen so that the conditions present in the brain will correspond to nonpermissive conditions.

An example of a suitable conditionally immortal oncogene is that which expresses the non-DNA binding, temperature-sensitive T antigen; a description of which may be found in US-A-5688692 or WO-A-97/10329.

If non-immortal cells are used then these may be maintained *in vitro* in culture media with the addition of growth factors as disclosed in WO-A-92/11355 and WO-A-93/18137.

The gene which is used to confer conditional immortality may be incorporated into cells after extraction from the bone marrow of an animal.

The cells used in the treatment of humans should preferably be derived from human cells to reduce problems with immune rejection. This requires the extraction of cells from the bone marrow of a human.

However, the cells do not necessarily have to be conditionally immortal, and may be obtained directly from the patient to be treated.

To treat a patient it is generally of assistance to know where damage has occurred in the brain. Once the existence of damage has been established, whether it be in one isolated area or in several areas, treatment by implantation of cells into the damaged area may be carried out. In many cases, however, the location and/or type of damaged tissue may be unknown or only poorly

characterised. For example, neurodegenerative diseases may lead to widespread damage to different types of cells. Treatment of such damage is still possible and is assisted by the ability of the haematopoietic stem cells to migrate extensively once transplanted and to seek out damaged tissue. The stem cells may be transplanted at a single site, or preferably at multiple sites, and may be able to migrate to the site(s) of damage and, once there, differentiate in response to the local microenvironment, into the necessary phenotype or phenotypes to improve or restore function.

After treatment the progress of the patient may be monitored using sensory, motor and/or cognitive tests and/or, if desired, tests which monitor brain activity in selected areas of the brain. For example, tests for cognitive function may be performed before and after transplantation.

Preferably, treatment will substantially correct a sensory, motor and/or cognitive deficit (behavioural and/or psychological deficits). However, that may not always be possible. Treatment according to the present invention and with the cells, medicaments and pharmaceutical preparations of the invention, may lead to improvement in function without complete correction. Such improvement will be worthwhile and of value.

The number of cells to be used will vary depending on the nature and extent of the damaged tissue. Typically, the number of cells used in transplantation will be in the range of about one hundred thousand to several million. Treatment need not be restricted to a single transplant. Additional transplants may be carried out to further improve function.

To study the transplantation in animal models the tests described in Hodges, *et al*, Pharmacology, Biochemistry and Behaviour (1997) 56(4):763-780 may be used. One test utilises rats in which the technique for four-vessel occlusion (4 VO), simulating human heart attack, causes relatively circumscribed and specific damage to the CA 1 pyramidal cells of the dorsal hippocampus, along with a cognitive deficit manifest as difficulty in locating a submerged and invisible platform in a swimming pool. This provides a model of cognitive dysfunction occurring as a consequence of a common form of brain

damage, i.e., transient loss of blood supply to the brain, for example, as may occur during cardiac arrest.

Methods for transplantation of cells into humans and animals are known to those in the art and are described in the literature in the art. The term "transplantation" used herein includes the transplantation of cells which have been grown *in vitro*, and may have been genetically modified, as well as the transplantation of material extracted from another organism. Cells may be transplanted by implantation by means of microsyringe infusion of a known quantity of cells in the target area where they would normally disperse around the injection site. They may also be implanted into ventricular spaces in the brain. If implanted into the neonate then they may disperse throughout the entire brain.

The phrase "intracerebral transplantation" used herein includes transplantation into any portion of the brain. Transplantation is not restricted to the front and larger part of the brain.

The utility of the present invention has now been reported independently in Chopp *et al*, Society for Neuroscience (1999), Vol. 25, Abstract No. 528.2. This Abstract was published after the priority date of the present Application and details the intracerebral transplantation of haematopoietic stem cells in mice.

As detailed in the Abstract, adult mice were subjected to middle cerebral artery occlusion (MCAo), and cultured haematopoietic stem cells (infused with growth factor) were transplanted into the ischaemic striatum (4 days after MCAo). Cell type specific markers were used for identification of the donor cells on transplantation. The results showed that donor cells survived transplantation and were morphologically detectable in the ischaemic striatum, exhibiting the phenotype of neuronal and astrocyte cells.

Suitable excipients, diluents and carriers will be apparent to the skilled person and formulations suitable for intracerebral transplantation will also be apparent.

The stem cells of the present invention may be genetically transformed to express a heterologous gene product. In particular, a therapeutic gene product that exerts its effect at the site of damage. Examples of suitable gene products are disclosed in US-A-5958767.

CLAIMS

1. Use of a haematopoietic stem cell in the manufacture of a medicament for the treatment of a sensory, motor and/or cognitive deficit.

2. Use according to claim 1, for intracerebral transplantation into a damaged brain.

3. Use according to claim 1 or claim 2, wherein the treatment is for Alzheimer's disease, Parkinson's disease, Korsakoff's disease or Creuzfeld-Jacob disease.

4. Use according to any preceding claim, wherein the haematopoietic stem cell is conditionally immortal.

5. Use according to claim 4, wherein the cell comprises a temperature sensitive oncogene which is not expressed at a temperature above 35°C.

6. Use according to claim 5, wherein the oncogene expresses the SV40 T-antigen.

7. Use according to any preceding claim, wherein the haematopoietic stem cell is genetically transformed to express a therapeutic heterologous gene product.

8. A method for treating a sensory, motor and/or cognitive deficit, comprising the intracerebral transplantation of haematopoietic stem cells.

9. A method according to claim 8, wherein the cells are as defined in any of claims 4 to 7.

USA

DECLARATION AND POWER OF ATTORNEY

As a below-named inventor, I hereby declare that my residence, post office address and citizenship are as stated below next to my name; I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of subject matter which is claimed and for which a patent is sought on an invention entitled
TRANSPLANTATION OF HAEMATOPOIETIC CELLS

the specification of which ☐ is attached hereto or

☒ was filed on 23 FEB 2000 as United States Application Number or PCT International Application Number PCT/GB00/00636 and was amended on (if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56. I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for a patent or inventor`s certificate, or PCT international application having a filing date before that of the application on which priority is claimed:

Prior Foreign Application Number(s)	Country	Foreign Filing Date	Priority Not Claimed	Certified Copy Attached? YES	NO
9904281.4	GB	24 FEB 1999	☐	☐	☐
			☐	☐	☐
			☐	☐	☐

As a named inventor, I hereby appoint the following registered practitioner(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:
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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C 1001 and that such willful false statements may jeopardise the validity of the application or any patent issued thereon.

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